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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,049	01/17/2006	Kristen E. Belmonte	PU60400	6150

20462 7590 09/19/2008

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EXAMINER	
O'DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
09/19/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/565,049	BELMONTE ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-13 and 15-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-13, 15-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/10/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-4 and 6-13, 15-21 are pending in the application.

2. This application is a national stage of PCT/US2004/023042 filed on July 16, 2004 which claims priority to U.S. Provisional Application No. 60/488,061 filed July 17, 2003.

Response to Arguments

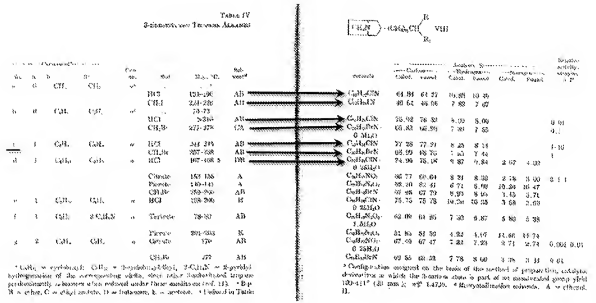
3. Applicant's arguments filed on July 10, 2008 have been fully considered but they are not persuasive. Zirkle who worked at Smith-Kline French, filed and received the U.S. patent and later published the results in the *Journal of Medicinal & Pharmaceutical Chemistry*, **1962**, *5*, 341-356. These results show how to make the compound, and disclose the pharmacological activity of these compounds, namely that they inhibit acetylcholine induced response with activity greater than atropine. The applicant has attempted to suggest that the instantly claimed compound has no utility in the teaching of Zirkle to quote the remarks:

"Table IV referenced on page 352 contains no biological data. The prior table, on page 351 does contain biological data for 8 of the 25 compounds listed therein. The compound on page 352 is not one of those with data shown for it."

However these statements are factually incorrect. In fact compound VIIIc (the instantly claimed compound) was stated as taken directly from Zirkle to be "somewhat more active than atropine".

> Since, in general, the more potent atropine-like agents contain an oxygen function in addition to the amino or quaternary ammonium group, the high activity of olefin VIa and alkane VIIIc, which have neither an oxygen function nor a quaternary ammonium group, is especially noteworthy. Alkane VIIIc, a methylene analog of benztropine (Ic), was found to be somewhat more active than atropine and as active as benztropine in the *in vitro* assay.

Applicant's confusion may be due to a misinterpretation of the reference which was previously explained in the action. The Tables on pages 352 and 353 of the Zirkle reference are actually one table. It is clear from the discussion in the paper and the biological data (far right column) that the VIIIc compound is the most potent. The examiner has tried to reproduce this below but the resolution is poor.



It is very clear when one reads it in the original journal and sees the pages facing one another. It may be necessary for the examiner to acquire a better copy for the applicant's representative so that it can be clearly seen.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The examiner would like to point

out that the rejection was made in view of Gillett, M. K.; Snashall, P. D. "Measurement of pharmacological antagonism produced by atropine in bronchi of normal and asthmatic subjects" European Respiratory Journal 1988, 1(1), 27-33 (abstract only). Apparently from the remarks the applicant has disregarded the abstract as a publication. The abstract is in fact a publication. The examiner need not provide the entire reference where everything relied upon is found in the abstract. The entire previously provided Gillett, M. K. et. al. abstract is reproduced below:

The bronchial response of normal and asthmatic subjects to increasing concns, of methacholine aerosol was measured by serial measurements of specific airways conductance (sGaw) in a body plethysmograph. On sep. days, the subjects were premedicated with 0.9% NaCl, inhaled atropine at 4 different doses, or i.v. atropine at 2 different doses. Cumulative log dose-response curves were constructed. The provocative dose of methacholine needed to cause a 35% fall in sGaw was measured from each curve (PD35). In normal subjects, approx, equal amts. of atropine given by the inhaled or i.v. routes produced mean dose ratios (PD35 after atropine: PD35 after saline) of almost identical value. However, in asthmatic subjects inhaled atropine (1.28 mg, 4.4 p, mol) produced a mean dose ratio 7.5 times greater than the mean value seen with i.v. atropine (1.0 mg, 3.46 p, mol). I.v. atropine (1.0 mg, 3.46 p, mol) produced a mean dose ratio of 18.3 for all subjects, compared to a value of 26 predicted from in vitro expts. The slope of the regression line for the relationship of log (dose ratio -1) vs -log atropine (Schild plot) for all subjects was -0.99. Obsd. results are compatible with the main actions of atropine being that of a competitive antagonist at the muscarinic receptor. The greater blocking effect of inhaled atropine in some asthmatics suggests that a higher concn, of atropine is achieved at the muscarinic receptor by the inhaled route in these subjects.

Clearly that is all that is needed. Here we have an old compound having biological activity that was "somewhat more active than atropine", and atropine being used in an inhaled form in experiments for lung disorders. It seems more than obvious to make an inhalable composition based on these references. For these reasons the claims to the composition are obvious.

With regard to the treatment of diseases, the specification has provided no actual data, but only prophetic assays, the examiner will maintain the enablement rejection for the reasons of record. The entire specification is speculation. To clarify the rejection of claim 6, which is drawn to "inhibiting the binding of acetylcholine to an acetylcholine receptor in a mammal in

need thereof", was made because we do not know what mammals need this compound since no physiological outcome has been associated with administering these compounds, thus no veterinarian or physician would know which humans should receive this material and the method cannot be practiced. It is true that no working examples are required, however in the highly unpredictable art of treating diseases undue experimentation would be required to practice the invention based on the disclosure which has no information at all. The prior art discloses the pharmacological activity of the compounds as anti-cholinergics, while the instant specification discloses nothing but rather states what was already known about these compounds and suggests experiments that might be done to find out more about them.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-4, 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zirkle et. al. U.S. patent 2,800,478 OR Zirkle et. al. *Journal of Medicinal & Pharmaceutical Chemistry*, **1962**, *5*, 341-356. in view of Gillett, M. K.; Snashall, P. D. "Measurement of pharmacological antagonism produced by atropine in bronchi of normal and asthmatic subjects" *European Respiratory Journal* **1988**, 1(1), 27-33 and U. S. Patent 6,608,055. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for

establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

A) Determining the scope and contents of the prior art.
B) Ascertaining the differences between the prior art and the claims at issue.
C) Resolving the level of ordinary skill in the pertinent art.
D) Considering objective evidence present in the application indicating obviousness or nonobviousness.

Zirkle et. al. U.S. patent 2,800,478 teaches the compounds of the current invention as a solid manipulated in air and thus inherently containing air (the composition would be composed of particles of the compound in a composition with air and such a composition would inhalable). In this publication the compound of claim 3, (3-endo)-3-(2,2-diphenylethyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide (applicant's name), Registry #: 106655-97-4 is synthesized and evaluated for its anticholinergic activity. The examiner believes this reference to be clearly enabled. Clearly solid compounds, or ethanol solutions of these compounds can be inhaled. They were hydrogenated in ethanol, and also recrystallized from ethanol or ethanol/ether).

nium hydroxide solution. The ether layer is separated and the solvent evaporated to give 1,1-diphenyl-2-(3-tropane)ethylene as a white crystalline solid which melts at 109.5–110° C. after recrystallization from acetone.

1,1-diphenyl-2-(3-tropane)ethane.—10 grams of 1,1-diphenyl-2-(3-tropane)ethylene dissolved in ethanol is hydrogenated over Raney nickel at 500 p. s. i. and 60° C. until hydrogen absorption ceases. After removal of the catalyst and evaporation of the solvent 1,1-diphenyl-2-(3-tropane)ethane is obtained as a colorless oil.

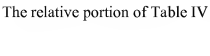
The hydrochloride of the base, formed in ethereal hydrogen chloride solution, melts at 244–245° C. after recrystallization from a mixture of ethanol and ether.

1,1-diphenyl-2-(3-tropane)ethane methobromide.—By allowing a mixture of 1 gram of 1,1-diphenyl-2-(3-tropane)ethane and excess methylbromide dissolved in acetone to stand at room temperature for several hours, the methobromide salt is obtained as white crystals. The product, after recrystallization from a mixture of ethanol and ether, melts at 257–258° C.

1,1-diphenyl-2-(3-tropane)ethane metho-p-toluenesulfonate.—An acetone solution of one gram of 1,1-diphenyl-2-(3-tropane)ethane and excess methyl p-toluenesulfonate is heated at reflux temperature for five minutes. By addition of ether to the cooled solution the quaternary ammonium salt is precipitated as a white solid.

1,1-diphenyl-2-(3-tropane)ethane maleate.—By adding 0.12 g. of maleic acid to 0.30 g. of 1,1-diphenyl-2-(3-tropane)ethane dissolved in ethanol and evaporating the resulting solution to dryness in vacuo the maleate salt of the base is obtained.

Zirkle et. al. *Journal of Medicinal & Pharmaceutical Chemistry*, **1962**, *5*, 341-356 teaches as per pg. 349 paragraph 2 "The tropane alkane derivatives listed in Table IV were obtained by reduction of the corresponding olefins. Olefin VII was hydrogenated smoothly over Raney nickel at room temperature and 4.2 kg./cm hydrogen pressure……" Compound VII is the olefin:



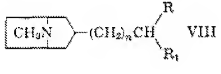
VII

The relative portion of Table IV is reproduced here:

TABLE IV
3-SUBSTITUTED TROPANE ALKANES

Compound[a] No.	n	R	R¹	Configuration	Salt	M.p., °C.	Solvent[d]
a	0	CH_3	CH_3	α[b]	...	...[c]	
					HCl	194–196	AB
					CH_3I	224–226	AB
b	0	C_6H_5	C_6H_5	α[b]	...	70–72	
					HCl	>310	AB
					CH_3Br	277–278	CA
c	1	C_6H_5	C_6H_5	α	HCl	244–245	AB
					CH_3Br	257–258	AB

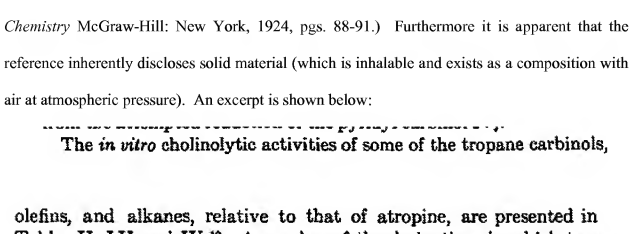
March 1962 3-SUBSTITUTED TROPANE DERIVATIVES. III 353



VIII

Clearly these compounds are simply salts of the free amines, and this operation (mixing with acid or alkyl halide/crystallizing) was not discussed in detail. It is relatively common for scientists not to discuss trivial procedures that all in the art are aware. This reaction of amines has been known for a very long time, for example a 1924 introductory lab text where the hydrochloride salt of methyl amine is prepared (Norris, James F. *Experimental Organic*

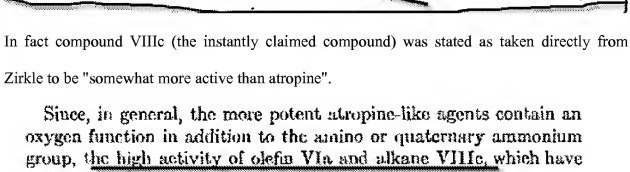
Chemistry McGraw-Hill: New York, 1924, pgs. 88-91.) Furthermore it is apparent that the reference inherently discloses solid material (which is inhalable and exists as a composition with air at atmospheric pressure). An excerpt is shown below:



The *in vitro* cholinolytic activities of some of the tropane carbinols, olefins, and alkanes, relative to that of atropine, are presented in Tables II, III and IV.[19] A number of the derivatives in which two carbon atoms separate R and R′ from the tropane ring are quite active agents, equalling or exceeding atropine in potency, whereas the lower and higher homologs of these derivatives are relatively inactive. The β isomer (IVf) of the diphenyl carbinol IVe and the unsaturated

(19) We are indebted to Mr. Edward Macko and his associates, of the Pharmacology Section of these Laboratories, for supplying these data.

In fact compound VIIIc (the instantly claimed compound) was stated as taken directly from Zirkle to be "somewhat more active than atropine".



Since, in general, the more potent atropine-like agents contain an oxygen function in addition to the amino or quaternary ammonium group, the high activity of olefin VIa and alkane VIIIc, which have neither an oxygen function nor a quaternary ammonium group, is especially noteworthy. Alkane VIIIc, a methylene analog of benztropine (Ic), was found to be somewhat more active than atropine and as active as benztropine in the *in vitro* assay.

While it is not clear what experiments were involved they were clearly administered in some fashion (composition or powder).

Regardless, since the compounds of the instant case are anticholinergics and atropine (an anticholinergic) has been used in inhalation formulations as taught by Gillett, M. K.; Snashall, P.

D. "Measurement of pharmacological antagonism produced by atropine in bronchi of normal and asthmatic subjects" *European Respiratory Journal* **1988**, 1(1), 27-33 and clearly the preparation of an inhalable formulation of these compounds is trivial undertaking as per U.S. patent 6,608,055 (see columns 9 & 10) it would be obvious to prepare a different formulation (a dry powder with additives, lactose, starch lines 15-20) and test them as anticholinergics as per the teaching of Zirkle.

According to another aspect, the present invention relates to the use of crystalline anhydrous tiotropium bromide as a medicament in the light of the pharmaceutical efficacy of the anhydrous form according to the invention. To prepare a medicament which can be inhaled, particularly an inhalable powder, which contains the anhydrous, crystalline tiotropium bromide described by the present invention, methods known from the prior art may be used. In this respect, reference is made, for example, to the teaching of DE-A-19 22 07. Accordingly a further aspect of the present invention relates to inhalable powders characterised in that they contain anhydrous, crystalline tiotropium bromide.

Because of the potency of tiotropium bromide, the powders for inhalation mentioned above preferably contain, in addition to the active substance, the following physiologically acceptable excipients. The following physiologically acceptable excipients may be used, for example monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, saccose, maltose), oligo- and polysaccharides (e.g. dextrane), polyalcohols (e.g. sorbitol, mannitol, xylitol), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another. Preferably, mono- or disaccharides are used, while the use of lactose or glucose is preferred, particularly, but not exclusively, in the form of their hydrates. For the purposes of the invention, lactose is the particularly preferred excipient, while lactose monohydrate is most particularly preferred.

Within the scope of the inhalable powders according to the invention the excipients which are characterised in that they contain anhydrous crystalline tiotropium bromide have a maximum average particle size of up to 250 μm, preferably between 10 and 150 μm, most preferably between 15 and 80 μm. It may sometimes seem appropriate to add finer excipient fractions with an average particle size of 1 to 9 μm to the excipients mentioned above. These finer excipients are also selected from the group of possible excipients listed hereinbefore.

Preferred inhalable powders containing the tiotropium bromide anhydrous according to the invention are characterised in that the excipient consists of a mixture of coarser excipient with an average particle size of from 17 to 50 μm, more preferably 20 to 30 μm, and finer excipient with an average particle size of 2 to 8 μm, more preferably 3 to 7 μm. The term average particle size here denotes the 50% value from the volume distribution measured with a laser diffractometer by the dry dispersion method. Inhalable powders wherein the proportion of finer excipient in the total quantity of excipient is 3 to 15%, more preferably 5 to 10%, are preferred.

One possible method of preparing these inhalable powders which are preferred according to the invention is discussed in more detail hereinafter.

After the starting materials have been weighed out, first the excipient mixture is prepared from the defined fractions of the coarser excipient and finer excipient. Then the inhalable powders according to the invention are prepared from the excipient mixture and the active substance. If the inhalable powder is to be administered by means of inhalettes in suitable inhalers, the preparation of the inhalable powders is followed by the production of the capsules containing the powder.

The inhalable powders according to the invention are prepared by mixing the coarser excipient fractions with the finer excipient fractions and subsequently mixing the resulting excipient mixtures with the active substance.

In order to prepare the excipient mixture the coarser and finer excipient fractions are placed in a suitable mixing container. The two components are preferably eddied through a screening granulator with a mesh size of 0.1 to 2 mm, most preferably 0.3 to 1 mm, even more preferably 0.3 to 0.6 mm. Preferably the coarser excipient is put in first and then the finer excipient fraction is added to the mixing container. In this mixing process the two components are preferably added batchwise, with half the coarser excipient being put in first followed by finer and coarser excipient added alternately. It is particularly preferable when preparing the excipient mixture to screen the two components in alternate layers. Preferably this screening of the two components takes place in 15 to 45, more preferably in 20 to 40 alternate layers. The mixing of the two excipients may take place while the two components are being added. However, it is preferably not done until the layers of ingredients have been added.

After the preparation of the excipient mixture, this and the active substance are placed in a suitable mixing container. The active substance used has an average particle size of 0.5 to 10 μm, preferably 1 to 5 μm, more preferably 2 to 5 μm. The two components are preferably added through a screening granulator with a mesh size of 0.1 to 2 mm, most preferably 0.3 to 1 mm, even more preferably 0.3 to 0.6 mm. Preferably the excipient mixture is put in first and then the active substance is added to the mixing container. It is particularly preferable when preparing the excipient mixture to screen the two components in alternate layers. Preferably this screening of the two components takes place in 25 to 65, more preferably in 30 to 50 alternate layers. The mixing of the excipient mixture with the active substance may take place while the two components are being added. However, it is preferably not done until the layers of ingredients have been added.

The powder mixture thus obtained may optionally be passed through a screening granulator once again or several times more and then subjected to another mixing operation each time.

The inhalable powders obtained by the above method preferably contain about 0.001 to 2% tiotropium bromide in admixture with a physiologically acceptable excipient. Preferred are inhalable powders which contain 0.04 to 0.8% of tiotropium bromide in admixture with a physiologically acceptable excipient, characterised in that the excipient consists of a mixture of coarser excipient with an average particle size of 15 to 80 μm and finer excipient with an average particle size of 1 to 9 μm, the proportion of finer excipient in the total quantity of excipient being 1 to 20%. According to the invention, inhalable powders which contain 0.06 to 0.64%, more preferably 0.16 to 0.4% tiotropium bromide, are preferred.

If anhydrous crystalline tiotropium bromide is included in the inhalable powders mentioned above, these powder mixtures preferably contain 0.0012–2.12% of tiotropium bromide anhydrate. Also preferred are inhalable powders which contain between 0.048 and 0.95% of tiotropium bromide anhydrate. Of particular interest according to the invention are inhalable powders which contain 0.095 to 0.77%, more preferably 0.19 to 0.48% tiotropium bromide anhydrate.

The percentages mentioned within the scope of the present invention are always percent by weight.

An alternative, equally preferred embodiment for preparing inhalable powders containing tiotropium bromide anhydrate may also be prepared from inhalable powders formulated on the basis of the crystalline tiotropium bromide monohydrate. These contain between 0.0012 and 2.5%, preferably 0.05 to 1%, preferably 0.1 to 0.8%, more preferably 0.2 to 0.5% crystalline tiotropium bromide monohy-

Thus it is very clear that the instant claims recite an obvious variation of an old composition, a variation that was known in this very narrow field of anticholinergic agents. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a variation on the composition of Zirkle et. al. A person of ordinary skill in

the art would have been motivated to do so based on the teaching of Gillett et. al. showing that inhalable administration was a good route for the administration of anticholinergics. Moreover the preparation of such a composition would be trivial to prepare as per U.S. patent 6,608,055.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 6-13, 15-20 are rejected under 35 U.S.C. 112, first paragraph, for failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

(A) The breadth of the claims: The claims are broad and drawn to many conditions, respiratory and otherwise but that's not really the main concern here, the main concern its that

these compounds have not been shown to be useful for treating any disease. **(B) The nature of the invention:** This invention is drawn towards a method for treating diseases. **(D) The level of one of ordinary skill:** One of ordinary skill in the art of treating diseases or determining which drug to use for the treatment of a condition would be either a medical doctor or Pharm D. **(C) The state of the prior art:** While Zirkle states that these compounds are the preferred compounds of his study, and effective *in vitro* as anti-cholinergics (ibid. pg. 352-353), we don't know how these compounds behave *in vivo*.

(F) The amount of direction provided by the inventor and (G) the existence of working examples: While the applicant has provided descriptions of assays in the specification, and statements like "All data is given as mean +- standard error of the mean…"(pg. 7), the examiner cannot find the data in the specification. Statements like the one found on pg 9 line 14 "This experiment allows for the determination of duration of activity of the administered compound…" without actually providing a single piece of data lead the examiner to believe that these are mere recitations of possible experiments that could be performed with the compounds and that none were actually performed. No working examples exist. It is true as the applicant has pointed out that no requirement exists for in-vivo data, however only if some clear correlation exists between the in-vitro assay and the disease state. In fact in the instant case we have no in vitro assay? What is the in-vitro assay that was performed? Clearly one can come up with prophetic assays, that do little to ease the unpredictable nature of these experiments as delineated below. This is called a research proposal. The specification seems to be a proposal for research to be conducted to find out if the compounds are useful for treating various disorders. **(E) The level of predictability in the art and (H) the quantity of experimentation needed to make or use the**

invention: In the absence of this data we are left with an old compound that is an anticholinergic, however it is well known that there are many muscarinic receptor sub-types and even before the application was filed a review article (Lee, A.M. et. al. *Current Opinion in Pharmacology* **2001**, *1*, 223-229) tells us that at least five distinct subtypes of muscarinic receptor exist (M1-M5 in humans). Each one of these GPCRs has distinct tissue distribution, second-messengers and most-importantly ligand profile. All that we currently know about these compounds is that they inhibit the action of acetylcholine in a non-specific assay (given in 1962 the subtypes of muscarinic receptors were not known). Maybe these were organ bath assays with sheep vas deferens, pig heart or guinea pig ileum. We don't know, but it would be helpful to know the tissue type and animal. Even if we know the tissue type these receptors are of course GPCRs and the differences between the animal protein and those found in humans is sometimes substantial (more or less subtypes, or little homology). What creatures will be treated with these compounds? It was well known at the time of the invention that in order to be used in applicants claimed manner (a disease, and specifically a lung disease like COPD and asthma, claims 7-12), that the sub-type selectivity is very significant parameter to be determined in assessing the *potential* therapeutic benefit of a putative pharmaceutical. Lee, A.M. et. al. ibid. state on pg. 225:

> Nonselective muscarinic receptor antagonists
> Atropine, ipratropium and oxitropium are nonselective
> antimuscarinic drugs that successfully abrogate bronchoconstriction
> and airway hyperreactivity in humans; however,
> they bind M2 and M3 muscarinic receptors with equal affinity
> [5]. Since the M2 subtype is an inhibitory prejunctional
> autoreceptor, blocking the M2 muscarinic receptor with a
> nonselective antagonist increases acetylcholine release and
> **may enhance bronchoconstriction.**
> Ipratropium (Boehringer Ingelheim Pharmaceuticals Inc.,

> California, USA) is the most widely used anticholinergic medication for airway disease. In guinea pigs, although it prevents bronchoconstriction in doses above 10 μg/kg (intravenous), it doubles vagally stimulated bronchoconstriction at lower doses. [48]. Paradoxical bronchoconstriction to ipratropium has been reported in humans [49,50], although no systematic study of M2 receptor blockade has been performed. Thus, the clinical efficacy of anticholinergics probably depends on the balance between M2 and M3 muscarinic receptor antagonism.

Thus we need to know several things: 1) Do these compounds antagonize muscarinic receptor subtypes found in the lungs? 2) What is the selectivity for receptor subtypes? 3) Are the effects *in vitro* correlated with *in vivo* activity? Number three is perhaps the most important factor, given the complexity of receptor sub-types, the possibly different affinities, rates of dissociation, etc. The real question is does it work as a therapy in a human? Again it must be reiterated that applicant has provided absolutely no data for these compounds, although Zirkle at Smith-Kline French in 1962 acquired some data, it is not clear that such data is correlated with treatment. We are provided with no answers to the questions above, thus it is very clear that one could not use this invention that has no working examples in this unpredictable art without undue experimentation. In regards to claim 6 which is drawn to "inhibiting the binding of acetylcholine to a[sic] acetylcholine receptor in a mammal in need thereof", we do not know what mammals need this compound since no physiological outcome has been associated with administering these compounds, thus no veterinarian or physician would know which mammals should receive this material and the method cannot be practiced.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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D.K.O.

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